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First generation vs. second generation long acting injectable antipsychotic drugs and time to relapse

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Abstract

Background: The development of long-acting injectable formulations (LAI) of second generation antipsychotic drugs (SGA) has been suggested to bring advantages over first generation (FGA) LAI. In this study we investigated the hypothesis that there was no difference in readmission rates in patients with schizophrenia started on SGA LAI vs FGA LAI.

Methods: Patients with a diagnosis of schizophrenia or schizoaffective disorder who were started on a SGA LAI while on an in-patient ward were identified through searching of the anonymised historical medical records at the South London and Maudsley NHS Foundation Trust. Patients starting FGA LAI matched for diagnosis, age and date of hospital admission were identified. Time to readmission, discontinuation of LAI or death was identified. Kaplan-Meier plots were generated for each group, and the difference between groups analysed using log-rank methods.

Results: One hundred and fifty seven patients were identified in each group. There was no difference in time to readmission, medication discontinuation or death in patients on SGA LAI vs FGA LAI.

Conclusions: We found no evidence of advantage in terms of maintaining response in SGA LAI vs. FGA LAI. Prescriber choice should be guided by other factors such as side effect profile, patient acceptability and price.

Introduction

The use of long acting injectable antipsychotic drugs (LAI) has been considered the gold standard in maintaining medication adherence and reducing the risk of relapse in patients with schizophrenia, although evidence for this is dependent upon the type of study performed, with clinical trials tending to show less benefit of LAI over oral antipsychotic drugs when compared to more naturalistic designs.^{1, 2}

The recent development of LAI second generation antipsychotic drugs (SGA) bring the promise of the advantage of enhanced medication adherence compared to oral antipsychotic drugs with the potential for lower movement-related side effects to first generation antipsychotic drugs (FGA).³ Studies of specific SGA LAI have shown reduced risk of hospitalisation vs. oral antipsychotics for paliperidone and aripiprazole, but not for risperidone depot.⁴⁻⁶ A large study comparing risperidone depot vs. FGA LAI did not find any difference in all cause discontinuation or hospitalisation in either group.⁷

In this study we aimed to investigate time to relapse in patients treated with SGA LAI vs FGA LAI in patients with schizophrenia or schizoaffective disorder admitted to the South London and Maudsley Trust.

Method

We used the Clinical Record Interactive Search (CRIS), a searchable anonymised database containing the clinical records of all patients registered with the South London and Maudsley NHS Foundation Trust (SLaM). This database includes information on over 220,000 patients; while the system was set up in January 2007, some patient data has been added retroactively, with the earliest patient data being from 1996. Ethical approval for research using CRIS as a database for secondary analysis has been obtained from Oxford Research Ethics Committee C.⁸

We identified patients with schizophrenia or schizoaffective disorder with no previous history of LAI treatment who were initiated on SGA LAI while they were admitted to hospital or under home treatment team up to February 2017. Search terms for SGA LAI were aripiprazole depot (Abilify Maintena), olanzapine embonate (ZypAdhera), paliperidone (Xeplion) and risperidone depot (Risperidone Consta). We then identified patients matched for diagnosis, age (\pm 5 years), gender, ethnicity and date of admission (\pm 6 months) with no previous history of LAI treatment who were started on FGA LAI while they were admitted to hospital or under home treatment team. Search terms for FGA LAI were fluphenazine decanoate (Modecate), haloperidol depot (Haloperidol Decanoate), pipotiazine palmitate (Piportil depot) and zuclopentixol decanotate (Clopixol). For each group we measured number of psychiatric in-patient days prior to the index admission and their illness length, estimated as the total time they had been under the care of SLaM NHS Trust. We measured the time from discharge until they stopped or switched medication, or until their next hospital admission, admission to home treatment team, or death, which were all classed as end-points for the purpose of the survival analysis. Lastly, we measured the number of face to face contacts that each patient had during the time they were on the depot medication.

Data were analysed using R version 3.3.2, using the “survival” package. Kaplan-Meier curves for the two groups were generated, and the difference between survival curves for FGA LAI and SGA LAI was determined using the G-Rho family of tests (log-rank) implemented in the “survdiff” function.⁹ A post-hoc analysis of the difference in survival curves for individual antipsychotics within the SGA and FGA LAI groups was also performed using the same statistical method.

Results

One hundred and fifty seven patients were identified in each group. Demographic details are detailed in Table 1. Patients in the FGA and SGA LAI groups did not differ in terms of days of hospitalisation prior to their index admission, but patients in the SGA LAI group had a significantly longer history of illness (4.95 vs. 3.97 years - $p=0.048$ – Table 1). In the FGA LAI group patients were

treated with zuclopenthixol (n=77), pipotiazine (n=14), haloperidol depot (n=19), flupentixol (n=43) and fluphenazine (n=4). In the SGA LAI group, patients were treated with risperidone depot (n=90), paliperidone (n=49), aripiprazole depot (n=16) and olanzapine depot (n=2).

Eighty-nine patients in the SGA LAI group and 95 in the FGA LAI group reached an end-point during the period of study (Figure 1). There was no significant difference in time to end-point in either group ($p=0.921$). There was also no difference in number of face to face contacts with services between either group following discharge from hospital (SGA = 136.1 vs. FGA = 121.6, $p = 0.386$). Due to the fact that risperidone depot requires more frequent dosing, we analysed the data excluding the patients on risperidone depot, but found that there was still no difference in time to end-point for the FGA vs. SGA LAI groups (Chisq = 1.4, $df = 3$, $p = 0.244$). With post-hoc testing, there was no difference between any of the FGA LAI antipsychotics in terms of time to end-point ($p=0.595$). In the SGA LAI group there was a significant difference between different antipsychotics, with those treated with paliperidone and aripiprazole depots having a lower than expected number reaching end-point during the study compared to those on risperidone and olanzapine depots (Chisq=8.2, $df=3$, $p=0.04$; Table 2).

Discussion

In this study, we did not find any evidence for a difference in medication discontinuation, readmission rates or time to readmission between patients with schizophrenia or schizoaffective disorder treated with FGA LAI and SGA LAI. This suggests that there is no advantage in terms of maintaining response in choosing either an FGA vs. an SGA LAI and prescriber choice should therefore be guided by other factors such as side effect profile, patient acceptability and price.

Post-hoc testing was suggestive that paliperidone and aripiprazole depot may have a favourable profile in terms of medication discontinuation or time to readmission compared to other SGA LAI. These findings have not been previously reported and is worthy of further research. A previous study of haloperidol depot vs. paliperidone found no difference in time to relapse,¹⁰ although this study

used a clinical trial methodology rather than a naturalistic design and so may not be representative of real world experience. A recent systematic review comparing aripiprazole depot with paliperidone depot concluded that aripiprazole had advantages in terms of discontinuation and efficacy.¹¹ Further well designed studies will be required to investigate these hypotheses further.

Although this study has strengths in that it uses naturalistic data acquired from clinical practice, and the patients were closely matched on relevant clinical and demographic characteristics, it was dependent on the quality, detail and timing of data entry into the clinical records. While the dates and times of hard end-points such as admission and death are likely to be accurate, the time to discontinuation of medication is more prone to error due to differences in clinical record keeping, and so may have been underestimated. In addition, selection of LAI was down to individual clinician choice, and so may have been a source of bias as paliperidone LAI has been found to be prescribed in patients with longer and more frequent hospital admissions.¹² In the current study, we found that length of time with the Trust was longer in patients prescribed an SGA LAI, suggesting that the SGA LAI group had a longer duration of illness, although the mean number of hospitalisations per year did not differ between the two groups.

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Table 1: Group characteristics of patients started on FGA LAI and SGA LAI.

	SGA	FGA	P
Mean(SD) age (years)	38.5(11.7)	38.9(12.7)	0.8
Gender (F/M)	65/92	65/92	1
Diagnosis (F20, F22, F25)	144,2,11	144,2,11	1
Mean(SD) length of illness prior to depot (years)	4.95(4.21)	3.97(4.54)	0.048
Mean(SD) number of in-patient days per year prior to index admission	7.37(20.5)	9.16(39.7)	0.62
Mean length of index hospital stay (d)	127.1 (204.1)	143.6 (213.2)	0.5
Ethnicity (African, Caribbean, Black, Mixed, British, Other White, Other)	45,19,39, 1, 33, 14, 6	45,19,39, 1, 33, 14, 6	1
End point (none, medication stop or change, home treatment team, admission, death)	68,15,13,55,6	63,9,15,68,3	0.22

Table 2: Stratified log-rank analysis for SGA LAI study end-points. Observed and expected number of patients reaching study end points in patients on each LAI are shown.

	n	Observed End Points	Expected End Points
Aripiprazole	16	5	8.79
Olanzapine	2	2	0.73
Paliperidone	49	18	25.453
Risperidone	90	64	54.025

Figure 1: Kaplan-Meier plot of time to end-point for patients with schizophrenia treated with FGA LAI (FGA) or SGA LAI (SGA).

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